Preparation and Characterization of Formulations in a High Throughput Mode

Inventors: Stephen Bysouth, Sid Hite, Amrish Bohara, John Hammond, Karin Bergström, Rowena Landham and Ingrid Lukkari

Field of the Invention

This invention relates generally to an automated robotic system for the production and testing of formulations at a very high throughput. More specifically, it is an integrated system of hardware and software capable of preparing and evaluating hundreds of dispersed multi-phase solutions per day. The system can process formulations rapidly in an automated way and enable very flexible formulation recipes to be introduced. Up to 1200 formulations on the 1 to 20 mL scale can be made per day. This includes tracking of processes from start to finish and the integration of analytical data with the as-designed and as-formulated experimental results. Materials and consumables can be distributed from storage systems to the work stations where dispensing of ingredients in various states can be performed, including solids, liquids, gels, pastes, suspensions and waxes. The emulsions, dispersions, and/or solutions formed can be characterized using methods including phase diagnosis, turbidity analysis, viscosity and particle sizing. The modular system allows future processes and tests to be added, either to a station, or as a new station.

Background of the Invention

Formulation chemists in the Surface Actives Ingredients (surfactants) and agrochemical markets realize the potential for applying Design of Experiments (DOE) methods to assess the impact of many variables on the performance, shelf-life, delivery characteristics, contamination susceptibility, and customer satisfaction of their products. Due to the complexity of the formulation recipes and the number of variables to be evaluated, DOE techniques generate matrices of tens of thousands of experiments that must be conducted to explore and refine the experimental space for these products. The shear number of experiments required renders typical bench chemistry techniques ineffective. The invention described herein provides the formulation chemist with a means of tackling these large DOE matrices in an automated fashion.

The Summary of the Invention is followed by a Detailed Description of the system. Finally, a Process Description provides step-by-step preparation and testing methodologies for a typical Solution in Water (SL) recipe and a Suspension Concentrate (SC) formulation recipe that is prepared and tested on the invention.

Summary of the Invention

The invention is an automated robotic system for the production and testing of formulations at a very high throughput. It is an integrated system of hardware and software capable of preparing and evaluating hundreds of dispersed multi-phase solutions per day. The system can formulate aqueous solutions (SL), oil in water emulsions (EW), suspo-emulsions (SE), micro capsule suspensions (CS), micro-emulsions (ME), and suspension concentrates (SC) at the 1 ml to 25 ml scale. The system can process emulsions rapidly in an automated way and enable very flexible formulation recipes to be introduced.

The system allows chemists to generate experimental samples of varying recipe and method to be conducted in parallel with projected throughput of up to 1200 formulations processed and characterized per day. Materials and consumables can be distributed from storage systems to the work stations where dispensing of ingredients in various states can be performed, including solids, liquids, gels, pastes, suspensions and waxes. The emulsions formed can be characterized using methods including phase diagnosis, turbidity analysis, viscosity and particle sizing using automated test equipment. An integrated module can also perform Tank Mix Compatibility testing in high throughput mode. The modular system allows future processes and tests to be added, either to a station, or as a new station. The software capability includes tracking of processes from start to finish and the integration of analytical data with the as-designed and as-formulated experimental results.

It is an object of the present invention to provide an automated robotic system for the production and testing of formulations.

It is a further object of the present invention to provide a system for the research, development, manufacture, and sale of products for use in agriculture, horticulture, forestry and protection during transport or storage or use of the harvested products of agriculture, horticulture

or forestry and the treatment of the environment to combat infestations of pests harmful to public health, safety or convenience.

It is a further object of the present invention to provide such a system for the discovery and development of crop protection or crop enhancement products and products for the treatment of the environment to combat infestation of pests harmful to public health, safety or convenience.

It is a further object of the present invention to provide such a system for the research, development, manufacture and/or sale of surfactants, fatty acids and rheology control agents in formulations for fabric care, personal care, textile, mining, mineral coating, asphalt, petroleum, fuels, viscose, cleaning, building, coatings, paper processing and manufacture and in all applications of nitrogen derived surfactants.

Brief Description of the Drawings

Figure 1 illustrates rack and vial storage system **100.**

Figure 2 illustrates consumables store **200.**

Figure 3 illustrates robotic arm **300.**

Figure 4 illustrates solid dispensing station **400.**

Figure 5 illustrates an embodiment of liquids, suspensions, gels and meltables dispense station **500.**

Figure 6 illustrates normal liquids dispensing and pipetting, and characterization station **600.**

Figure 7 illustrates mixing or homogenizing station **700.**

Figure 8 illustrates flexible arm station **800** used in alternative embodiment.

Figure 9 illustrates comminutor station used in an alternative embodiment **900.**

Figure 10 illustrates phase stability and cloud point station **1000.**

Figure 11 illustrates buffers **1100.**

Figure 12 illustrates dispensing, pipetting, and characterization station **1200**, included in alternative embodiments.

Figure 13 illustrates an exemplary flow diagram for system set-up.

Figure 14 illustrates flow diagram of experiment for preparing and testing Solution in Water (SL) formulation.

Figure 15 illustrates flow diagram of experiment for preparing and testing Suspension Concentrate (SC) emulsion formulation.

Figure 16 illustrates an embodiment of the present invention comprising rack and vial storage system **100**, consumables store **200**, robotic arm **300**, mixing or homogenizing station **700**, phase stability and cloud point station **1000**, buffers **1100**, and dispensing, pipetting, and characterization station **1200**.

Figure 17 illustrates an embodiment of the present invention comprising rack and vial storage system **100**, consumables store **200**, robotic arm **300**, solid dispensing station **400**, liquids, suspensions, gels and meltables dispense station **500**, liquids dispensing and pipetting and characterization station **600**, mixing or homogenizing stations **700**, flexible arm station **800**, comminutor station **900**, phase stability and cloud point station **1000**, and buffers **1100**.

Detailed Description of the Invention

An automated robotic system is disclosed herein for the production and testing of formulations at a very high throughput. In a preferred embodiment, a run is considered to be the operation of the system over a 24 hour period, including an approximately 20 hour operation period and an approximately four hour set-up period. Further, the disclosed, preferred embodiment is based upon the use of a 25 mL vial to hold about 10 mL of test formulation. The embodiment disclosed herein is disclosed for illustrative purposes only, alternative embodiments are envisioned.

Figure 1 illustrates rack and vial storage system **100**, comprising rack **102** and vial **104**. Vials are of the order of 25 mL, and 24 mm diameter, 73 mm high. They are racked in racks with a 'well-plate' foot-print containing 6 vials per rack. Each vial is bar coded and each rack is bar-coded. As these are custom racks, there is likely no cost differential between having plastic racks molded or machined from metal. In fact, metal racks can provide a simpler and faster means to

heat the vials, because placing a rack of vials on a hot-plate is faster than transferring vials from a rack to a heating block. In this instance too, less space is needed on a robot deck, as empty racks are not generated, diminishing the need for storage.

Figure 2 illustrates consumables station **200**. These are used to supply the materials needed for a run including vials, pipette tips and, optionally, materials to be dispensed. The number and size of the storage systems will depend on the manufacturer, vial size and functions as above, selected by the customer.

There are many manufacturers of these storage systems or stations (for example, Zymark, CRS, TomTek, STRobotics, etc.,) and custom versions can be obtained. Standard models work with the ubiquitous 'Well-Plates' and it is intended that the system disclosed herein will rack materials in the same format, be it vials, pipette tips or even solids for dispensing. These racks can also be referred to as 'plates' but their height will not be a standard well plate height.

These stations are designed to store and present to an arm or gantry robot, individual plates in a defined position. At the beginning of a run they are loaded appropriately and at the end of a run, they contain finished formulations, grouped as needed (pass, fail, etc.,), along with empty racks and used source vessels, ready for unloading.

Capacity requirements are dependent upon the desired application. For example in one embodiment 2000 positions are provided to hold 1500 vials (leaving 500 empty) and in a second embodiment 1000 positions are provided with 600 vials (leaving 400 empty). Additionally, space is provided for consumables (for example 5000 pipette tips) and for compound supply.

Figure 3 illustrates robotic arm **300** showing arm **302** and rail **304**. There are many robotic arm manufacturers and the most suitable arm and manufacturer are selected during the design phase for each application. The robotic arm provides the transport connection between all the stations for making and characterizing the emulsions, by moving the racked vials between the stations as required. In some embodiments the system is augmented by a second arm. Where the system is not augmented by a second arm, the sole arm also has the task of loading individual vials into the mixing systems; this requires either a gripper tool change, or the design of a dual function gripper for both vial and rack handling.

Operation of the robotic arm can be considered to be divided into three parts: set-up, where materials and racks are dispersed about the system; run, where samples and supplies are transported during making of emulsions and; clean-up, where at the end of a run, dispersed material and samples are restored to their proper location. The use of such an arm enables 'random access' type of ordering of processes supplied by the stations around the rail. In a preferred embodiment, the robotic arm has the ability to read rack identity by bar codes.

Figure 4 illustrates solid dispensing station **400**. Such a station can be obtained from multiple manufacturers, including Chemspeed, Autodose and Flexiweigh. The platform is adapted to suit individual requirements. The dispense accuracy of each system is dependant on the material to be dispensed. Additionally, a representative sample must be dispensed from the container in terms of particle size and chemical composition. If required, sample conditioning such as grinding and sieving can be used to prepare the powders. Dispenses of 1 mg can easily be achieved and pre-treatment of the powders will increase both accuracy and precision.

The solid dispensing station **400** can accept racks of empty vials, or vials from other dispense stations in racks and can either be preloaded with materials for a run, or accept racks of materials to be dispensed. The station picks up either whole racks of vials or individual vials, places them on mass balance **402**, dispenses by weight, solids obtained from solid source hoppers **404** into each vial, returning the vials to the rack before placing the rack at the delivery/collection point. It also moves racks of materials to be dispensed from the delivery/collection point to the distribution point on the deck. The station also includes bar code reader **406**.

Figure 5 illustrates an embodiment of liquids, suspensions, gels and meltables dispense station **500**. This station is based upon a gantry or Cartesian laboratory robot. Again, there are many manufacturers of such systems for example the Gilson "Cyberlab" 230/240/400 type platforms. These robot systems allow up to six tools to be mounted on the tool head above the deck, and the deck can be fitted with custom equipment including sub-stations with other integral tools. In a preferred embodiment the tool head is fitted with devices such as, but not limited to: rack/plate gripper, vial and cap gripper, gel dispenser gripper if required, pipettor for small plastic disposable pipette tips, optional pipettor for glass disposable pipette tips, and vacuum canula for dispensing grinding beads.

Some tools can require more than one tool position. Some of these devices are multifunctional. For example, the vial gripper can also function as the gel dispenser gripper. Additionally, in varying embodiments, more than one size of pipette can be required for precision and accuracy in dispensing. It is envisioned that both 5 mL and 500 μL tips are used.

The deck is mounted with associated devices such as, but not limited to: movable gel dispensers **502;** rack or dispensing locations **504**; comminuting bead source **506**, pre-loaded with beads; bar code reader/decapper **508**; orbital shaker **510**; one or more heated blocks **512;** heated glass pipette tips **514**; second mass balance **516**; pipette-tip rack space **518**; liquid vial deck space to enable other sources of normal liquids to be placed on the deck; enough space to contain the racks (likely stacked) that have been emptied into other deck units; and trash collection chute **520** for pipette tips and vial caps. Bar code reader/decapper **508** is used for identifying and opening vessels that arrive capped. Mixtures requiring agitation, such as unstable suspensions, are delivered to orbital shaker **510** after decapping. Orbital shaker **510** is also used for mild mixing such as dissolution and with careful selection of the shaker, even more aggressive agitation can be achieved. Where needed, materials are placed to melt upon/within the one or more heated blocks **512,** the materials are then readied for dispensing. Heated glass pipette tips **514** can be preloaded to be heated for dispensing small quantities of meltables. Second mass balance **516** is used for confirming the dispense by weighing.

Because of the distribution of the tools on the head of such robots (where fixed tools are in fixed positions on the head), not all the deck space is accessible by all tools. Specifically, for example, in certain instances the right hand tool cannot reach the left hand side of the deck and visa versa. This limits the position and access for each tool to the bed. Alternatively, the gel, paste and high viscosity fluid dispensing or the meltables dispensing can require a separate station or sub station, especially when combined with mixing or when the quantities that should be dispensed, exceed 2 mL. When mixing is not required, the dispense volume can be confirmed using a balance. However, since order of addition and mixing do not allow the tip of any dispenser to contact the mixed formulation, the dispensing must be conducted without touch-off.

When a mixer is used with dispensing, the station includes a dedicated wash station in which the mixers are cleaned, along with a wash fluid reservoir, pumps, drainage and valves as required (specified during the design phase) mL and 500 μL tips are used.

Figure 6 illustrates normal liquids dispensing and pipetting, and characterization station **600**, which can be included in alternative embodiments. This station provides a pair of waste stations where two separated types of fluid can be pumped to waste, and can be preferred when fluids are incompatible. The tool head can be fitted with items such as: rack/plate gripper; vial, filter and cap gripper; pipettor for plastic disposable pipette tips; dispense needle attached to the off-deck dispensing pumps, valves and manifold; and dispense needle for dispensing a common wash fluid.

Again, some tools can require more than one tool position and in a preferred embodiment, some devices are multifunctional. As before, more than one size of pipette is required for precision and accuracy in dispensing. It is envisioned that both 5 mL and 500 μL tips would be used. Additionally, a pipettor suitable for more viscous samples can require a separate tool or replace those in the 5 mL tip rack.

The deck is mounted with devices, the number and position of which are dependent upon the application. The devices include but are not limited to the following: bar code reader/capper/decapper **602**; caps source; second pipette-tip rack space **604**; liquid vial deck space; second orbital shaker **606;** tank mix testing unit **608**; particle-sized injection port **610**; dilution port **611**; viscometry injection port(s) **612**; filtration device; filter elements source **614**; particle size detector **618;** viscometry detector(s) **620;** cap supply **622;** wash station **628;** bead collection **630;** trash **632;** photography system **624**, and particle microscopy system **638**.

The bar code reader/capper/decapper **602** is used for identifying and opening vessels that arrive capped and for closing vials before they are sent to storage. In a preferred embodiment, a source for about 2000 caps is provided. In a preferred embodiment, pipette-tip rack space **604** comprises a source of special slotted tips for aspirating the comminuted mixture from the beads. Liquid vial deck space enables other sources of normal liquids to be placed on the deck. Similarly, in a preferred embodiment, enough space is provided to contain the racks and to provide space for sorting sample vials into classes (e.g. once pass/fail criteria are applied). Orbital shaker **606** provides general mild to moderate mixing but is also used for Tank Mix Testing **608**. Samples are pipetted into the particle-size injection port **610**, the actual particle size detector **618** being mounted off deck. Dilution port **611** allows dilution of the formulation for particle photography. Viscometry injection port(s) **612** allow for measurement of viscosity at

different shear rates. Filtration devices allow for timing the filtration of tank mix test samples. Filter elements obtained from filter elements source **614** are used for the tank mix test. Photography system **624** is used for photographing the tank mix test filter surface.

Off the robot deck are mounted large components of processing or measuring devices, including but not limited to: particle size detector **618,** photography system **624,** viscometer measurement electronics **620,** valve and pump system **626** for dispensing small (10's of micro liters) volumes of samples with a 'majority solvent' flush to the dispense needle, and pump and source of common wash fluid **616** connected to its needle.

Figure 7 illustrates mixer/homogenizer station **700** with liquid addition. These station(s) have the ability to mix in both high and low shear mode in parallel. Stations **702** include a two axis (one vertical and one horizontal axes) Cartesian robotic system that can move up to six mixer/homogenizers **704** mounted in-line on an arm, between several rows of up to six (n x 6) vessels and to an ultrasonic wash station **706** and a rinse station **708**. Additionally, the vessels in which mixing is occurring can be heated or cooled via a temperature-controlled fluid jacket and a chiller/heater/circulator **710**. The mixers include hardware to mount 3 probes of 1/8" diameter with their working ends at the mixer blade. These probes can be for measuring pH or tubes for dispensing fluids into the mixture connected to a liquid addition unit **712** as determined by application requirements.

The mixer/homogenizer **704** preferred capabilities include: the ability to mix in high and low shear modes; the ability to determine some measure of torque such as current vs. speed to allow a crude measure of viscosity; and a head diameter of no more than 15 mm.

The liquid addition units **712** allow specific liquid(s) to be dispensed while mixing. The liquid addition units are built from common components available from companies such as Hamilton, Cavro, Rheodyne and Valco. The numbers of designs of such devices are infinite, and those described here should be thought of as proposals to meet defined needs with the understanding that other component combinations can provide the appropriate functionality.

In a first embodiment of a liquid addition unit, each of the mixer heads is provided with one supply tube, each supplied from a separate pump **714** and source bottle **716**. This allows the addition of up to six different liquids chosen by the mixer row position where the target vial is

loaded. These pumps are able to quantitatively dispense moderate and low viscosity materials (flow at room temperature).

In a second embodiment of a liquid addition unit, the mixer system is provided with two tubes along with a combination pH electrode. In a preferred embodiment an electrode of 1/8' diameter which includes the temperature probe, is used. Fluid is supplied to each mixer/homogenizer head, one at a time, from valves **718**. As described, it can be used for pH adjustment; however, it can also be used for dispensing other normal liquids if pH adjustment is not needed.

Additionally, off deck can be a pH multimeter **720** such as that available from NICO2000. Versions are available that accept up to 24 pH probes and 24 temperature probes.

Figure 8 illustrates flexible arm station **800** used in an alternative embodiment. Flexible arm **802** accepts racks of vials from the robot arm **302** delivery point and provides individual vials to capping/ decapping/bar code reading/cap supply station **804**. For mixing, if caps are present, they are removed and discarded in trash bin **806** and the vials placed in the appropriate mixer location **704**. Alternatively, caps can be put on the vial before it is placed in comminutor **902** by flexible arm **802**. After processing, flexible arm **802** moves the vials to the capping/decapping/ bar code reading/cap supply station **804** as needed and returns them to the appropriate racks.

Systems within reach of flexible arm **802** can include but are not limited to: transfer area for delivery and receipt of racks of vials **808**; rack storage space for emptied racks **810**; capping/decapping/ bar code reading/cap supply station **804** (vials only- not racks); if flexible arm **802** is used during the de-capping, trash chute **806**; off mixer station(s); and comminutor loading receptacle **904**. The reach of the robot chosen is dependent upon the dimensions of the system, specifically the rack storage space and the comminutor.

Figure 9 illustrates comminution station **900** used in an alternative embodiment. In this embodiment, planetary ball mill **902** is modified and small vials of about 25 mL are placed around the periphery of vial holders **906** to provide the comminution action required for up to 32 vials in parallel. Capped vials are delivered to the mill containing solids liquids and beads. The planetary action causes the beads to roll and 'fly' in the vial, causing grinding of the solid particles. After a prescribed time, the mill returns to defined stop position **908** and the vials are

extracted and racked by arm **802**. Before racking, the vials can be de-capped. Whether to de-cap depends on the future of the vial. Further, vials can be stored in the space provided and de-capping delayed to allow material to settle off the lid.

Figure 10 illustrates phase stability and cloud point station **1000**. Apart from torque feedback from the mixing stations, phase stability and cloud point station **1000** is the first station visited by most samples where characterization takes place. It is based on Cartesian robotic system **1002** such as provided by Gilson. In a preferred embodiment, the only tool on the head 1004 is gripper **1006**. This gripper has the ability to invert the vials if needed. Mounted on the deck are turbidity analysis instrument(s) **1008** such as Turbiscan (from Formulaction) or similar systems, bar code reader **1010**, heated/cooled zones **1012** and space for at least 3 racks. Samples are delivered in racks by arm **302**, and vials withdrawn and either placed in the heated/cooled zones and subsequently into the turbidity analysis instrument systems, or immediately into the turbidity analysis instrument systems where they are characterized for such properties as turbidity, phase separated, homogeneous, sedimentation, creaming, foaming etc. The ability to invert the vial just before measurement, also allows foaming and sedimentation to be studied. The vials are then removed and either placed back into the original rack, or sorted into 'pass' and 'fail' racks as determined by the selection criteria. Arm **302** then removes the racks of vials.

Figure 11 illustrates temperature buffers **1100**. Typically, such complex automated systems need space to buffer the stations to allow processes occurring at different times and speeds, to be synchronized. Each of solid dispensing station **400**; liquids, suspensions, gels and meltables station **500**; normal liquids dispensing and pipetting and characterization station **600**; flexible arm station **800,** phase stability and cloud point station **10000**; and alternate dispensing, pipetting, and characterization station **1200** naturally provides some buffer capacity and space in storage systems **100** that can also be available during an experimental campaign. However, additional space can be required. For example, two embodiments could include ambient and temperature controlled buffers **1102** and **1104**, respectively. Additionally, arm **302** is then the only service that the buffers would require as these buffers would be 'dumb'.

Figure 12 illustrates alternate dispensing, pipetting, and characterization station **1200**, which can be included in alternative embodiments. This station is based upon a gantry or Cartesian Laboratory Robot. Again, there are many manufacturers of such systems such as the

Gilson "Cyberlab" 230/240/400 type platforms. These robot systems allow up to six tools to be mounted on the tool head above the deck, and the deck can be fitted with custom equipment including sub-stations with other integral tools.

The tool head can be fitted with items such as: rack/plate gripper; vial and cap gripper; gel dispenser gripper; pipettor for plastic disposable pipette tips; pipettor for glass disposable pipette tips; dispense needle attached to the off-deck dispensing pumps, valves and manifold; and dispense needle for dispensing a common wash fluid

Again, some tools can require more than one tool position and in a preferred embodiment, some devices are multifunctional. As before, more than one size of pipette can be required for precision and accuracy in dispensing. It is envisioned that both 5 mL and 500 μL tips would be used. Additionally, a pipettor suitable for more viscous samples can require a separate tool or replace those in the 5 mL tip rack.

The deck can be mounted with the following associated devices, the number and position dependent upon the application: bar code reader/capper/decapper **1202**; caps source **1232**; pipette-tip rack space **1204**; balance **1206**; liquid vial deck space; particle-sized injection port **1208**; viscometry injection port(s) **1210**; drain wash station(s) **1212**; gel dispensers **1220**; orbital shaker **1214**; heated block(s) **1216** and heated pipette tips **1218**.

Bar code reader/capper/decapper **1202** is used for identifying and opening vessels that are capped and closing vials before they are sent to storage. In a preferred embodiment cap source 1232 provides a source for about 2000 caps. Balance **1206** is used for confirming the dispense by weight. Liquid vial deck space enables other sources of normal liquids to be placed on the deck. Similarly, in a preferred embodiment, enough space is provided to contain the racks and to re-order the vials into classes. Samples are pipetted into particle-sized injection port **1208.** Viscometry injection port(s) **1210** allow for measurement of viscosity at different shear rates. Orbital shaker with heating and cooling capability **1214** is where mixtures requiring agitation, such as unstable suspensions, are delivered after decapping. Orbital shaker **1214** can also be used for mild mixing such as dissolution. With careful selection of the shaker, even more aggressive agitation can be achieved. Materials are placed upon/within heated block(s) **1216** for melting. The materials are then readied for dispensing. Heated pipette tips **1218** can be preloaded and heated for dispensing small quantities of meltables.

The off deck is mounted with devices, including but not limited to: second particle size detector **1222** and flush system; second viscometer electronics **1224**; second valve and pump system **1226** for dispensing small (10's of micro liter) volumes of samples with a 'majority solvent' flush to the dispense needle; trash receptacle **1234;** dilution port **1236;** second particle microscopy system **1238,** and pump and source of common wash fluid connected to its needle **1228**.

In this embodiment, the gel, paste and high viscosity fluid dispensing or the meltables dispensing (See Figure 5) can require separate mixing station **1230**. When mixing is not required, the dispense volume is confirmed using balance **1206**. However, as order of addition and mixing do not allow the tip of any dispenser to contact the mixed formulation, the dispensing must be conducted without touch-off.

Process Description

The automated robotic system is designed to operate without manual interference for a minimum duration of, but not limited to, one day after it is initialized and loaded with relevant components (raw materials, consumables, vials and racks) in the set up phase. Each vial **104** in any given rack **102** represents a unique experiment and has its own set of parameters such as, but not limited to, number of components, type and quantity of each component, mixing time, comminution time, etc. The tool heads on solid dispensing station **400,** liquids, suspensions, gels and meltables dispense station **500,** normal liquids dispensing, and pipetting, and characterization station **600** and flexible arm station **800** are capable of handling both racks **102** and single vials **104**. However, arm **302,** used for transfer between stations in one embodiment, can handle only racks **102**. Hence, the vials **104** are always grouped together in racks **102** when being transferred between stations. Once on a station, vials **104** can be picked up by the tool head and taken to the required locations for processing.

The actual working of the system is described in this section with the help of two examples: 1/ experiment for preparing and testing Solution in Water (SL) emulsion formulation; and 2/ experiment for preparing and testing Suspension Concentrate (SC) emulsion formulation.

In the first example, the initialization and set up phase have also been elaborated upon to illustrate the steps involved in preparing the system for a batch of experiments.

Example 1: Experiment for preparing and testing Solution in Water (SL) emulsion formulation

The objective of this experiment is to prepare a clear formulation, within a certain pH range, containing one active ingredient and three different additives. Successful formulations are then further tested for their chemical and/or biological activity. The steps involved in this experiment are as follows:

1) Add additives in the vial
2) Add active ingredients in the vial
3) Add water in the vial
4) Mix at low shear for 30 seconds
5) Heat the mixture for 10 minutes at 60 °C
6) Mix at high shear for 2 minutes
7) Conduct phase analysis
8) Store the clear samples for 24 hours and reject others
9) After 24 hours, conduct phase analysis on stored samples
10) Store the clear samples for further analysis and reject others

In the current example, the component properties and quantities in one particular experiment are assumed to be as those described in the Table below.

Component	Type	Quantity (mL or g)
Additive 1	Low viscosity liquid	0.6
Additive 2	High viscosity liquid	0.6
Additive 3	Solid	0.6
Active ingredient	Low viscosity liquid	7.6
Water	Low viscosity liquid	1

Before the experimentation can begin, the system undergoes a set-up phase comprising of the following steps:

1) Load racks and vials in the rack and vial storage system **100**

2) Load consumables in consumables station **200**

3) Load components on appropriate stations

4) Transfer consumables to appropriate stations

The entire set-up procedure for the current experiment is represented in Figure 13 in the form of a work-flow diagram and is further elaborated herein.

Figure 13 illustrates the steps involved in the set-up phase of the system before experimentation can begin for preparing and testing Solution in Water (SL) emulsion formulation. The various steps involved in executing each block of the flow diagram are described below in detail, we note that this description is for illustration purposes only, various embodiments will necessitate various steps in various orders as will be readily seen by the experienced practitioner.

Start system initialization step **1302**, is the first step of initialization. Here, the entire system is switched on and a primary system check is conducted by the operator.

The next step is loading racks and vials step **1304,** where the required number of racks **102** and vials **104** are loaded in rack and vial storage system **100**.

In loading consumables step **1306** all consumables such as but not limiting to pipette tips are loaded in consumables storage system **200**.

In load active ingredient step **1308,** active ingredient(s) are loaded on liquid dispensing, pipetting, characterization station **600**. In a preferred embodiment, the active ingredients are loaded through the bottles connected to valve and pump system **626**.

In load additive one, step **1310,** additive one is loaded on liquids, suspensions, gels, and meltables dispensing station **500.** In a preferred embodiment loading occurs at rack or dispensing locations **504**.

In load additive two, step **1312**, additive two being high viscosity liquid, can be dispensed by movable gel dispensers **502** on liquids, suspensions, gels and meltables dispense station **500** and hence are loaded in one of gel dispensers **502**.

In load additive three, step **1314,** additive three being a solid, is dispensed at solid dispensing station **400**. It is loaded in one of solid source hoppers **404** and can be placed either directly on solid dispensing station **400** or in rack **102** in consumables storage system **200**. From consumables storage system **200**, rack **102** containing hopper **404**, can then be picked up by robotic arm **302** and transported on rail **304** to solid dispensing station **400**.

In load water step **1316,** water is loaded on liquid dispensing, pipetting, characterization station **600** through a bottle(s) connected to valve and pump system **626**.

In transfer consumables step **1318**, consumables such as but not limited to pipette tips, are picked up from consumables storage system **200** by robotic arm **302** and transferred on rail **304** to liquids, suspensions, gels, meltables dispense station **500** and normal dispensing, pipetting, characterization station **600**.

Finally, in system initialization complete step **1320,** after all components are loaded and consumables transferred, the system is ready to start the experiments.

Figure 14 illustrates the flow diagram of the experiment for preparing and testing Solution in Water (SL) formulation. The various steps involved in executing each block of the flow diagram are described below in detail. As before, we note that this description is for illustration purposes only, various embodiments will necessitate various steps in various orders as will be readily seen by the experienced practitioner.

At start of experiment step **1402**, rack **102** containing as many as, but not limited to, six empty vials **104** is picked up by arm **302** and transferred to rack **102** entry point on liquids, suspensions, gels, meltables dispense station **500**. From here, it is moved to rack or dispensing locations **504** by the tool head on liquids, suspensions, gels and meltables dispense station **500**.

In add additive one, step **1404,** the tool head picks up vial **104** from rack **102,** takes it to barcode reader/ decapper **508** for barcode scanning and puts it back in rack **102**. Based on the barcode, the control software determines the component, in this case additive one, to be dispensed in vial **104**. For the current experiment, the tool head picks up a disposable pipette

from pipette-tip rack space **518**, aspirates 0.6 mL of additive 1 and dispenses it in the appropriate vial **104** in rack **102**. The tool head then moves above the trash collection chute **520** to dispose of the pipette tip.

In add additive two, step **1406,** additive two being a high viscosity liquid, is dispensed gravimetrically. The tool head transfers vial **104** from its rack **102** to mass balance **516**, which is then initialized and tare weight determined by the control software. The tool head then picks up movable gel dispenser **502** containing additive two, brings it over vial **104** and dispenses the additive two in discreet shots of 0.1 g until the balance registers 0.6 g. It then takes movable gel dispenser **502** back to its location and transfers vial **104** back in rack **102**. When all the dispense tasks of the liquids, suspensions, gels, meltables dispense station **500** are completed, rack **102** with all its vials **104** is transferred to rack **102** exit point on liquids, suspensions, gels and meltables dispense station **500**.

In add additive three, step **1408,** rack **102** is picked up from rack **102** exit point on liquids, suspensions, gels and meltables dispense station **500** by arm **302** and transferred to the rack **102** entry point of solid dispensing station **400** for dispensing additive three. From there, vial **104** is first taken to barcode reader **406** for barcode scanning and then placed on mass balance **402** by the tool head on solid dispensing station **400.** From the barcode, the control software confirms the solid to be dispensed, in this case additive three, which needs to be dispensed in vial **104**. In the current example, hopper **404** containing additive three is picked up by the tool head and 0.6 g of additive three is added in vial **104** on mass balance **402**. When all solid dispensing tasks are completed, rack **102** is transferred to rack **102** exit point on solid dispensing station **400**.

In add active ingredient step **1410,** arm **302** picks up rack **102** from the exit point on solid dispensing station **400** and transfers it to rack **102** entry point on normal liquids dispensing and pipetting, and characterization station **600**. The tool head picks up rack **102** from entry point and transfers it to rack **102** buffer zone. There, 7.6 mL of active ingredient is added volumetrically in the vial **104** by the needle on tool head from the active ingredient reservoir connected to valve and pump system **626**.

In add water step **1412,** after adding active ingredient, the needle on tool head is rinsed in wash station **628** and then 1 mL of water is dispensed from the water reservoir connected to

valve and pump system **626**. Rack **102** is then moved to rack **102** exit point on normal liquids dispensing and pipetting, and characterization station **600**.

In mix vial step **1414,** arm **302** transfers rack **102** from exit point on normal liquids dispensing and pipetting, and characterization station **600** to rack **102** entry point **808** next to flexible arm **802**. Flexible arm **802** moves rack **102** from there to the rack storage space for emptied rack **810**. Vial **104** is picked up by flexible arm **802**, taken to barcode reading station **804** for identification and then placed on mixer/homogenizer station **704** on mixer/homogenizer station **700**. Parallel mixing stations **702** moves over up to six vials **104** placed on six parallel mixer/homogenizer stations **704**, moves vertically down till mixers are in vials **104**, and then starts mixing at low shear for 30 seconds. When the mixing time is complete, six parallel mixer/homogenizer stations **704** move vertically up till they are out of vials **104**, move to the ultrasonic bath **706** to get washed and then move to the rinse station **708** to get rinsed. The vials are moved back from mixer/homogenizer stations **704** to rack **102** in the rack storage space for emptied rack **810**. Rack **102** is then moved to rack **102** exit point.

In heat vial step **1416,** arm **302** transfers rack **102** from rack **102** exit point on flexible arm station **800** to the temperature buffers **1100** where it is kept at 60 °C for 10 minutes.

In adjust pH step **1418,** after 10 minutes, rack **102** is again transferred to rack **102** entry point **808** next to flexible arm **802**. Flexible arm **802** moves rack **102** from there to the rack storage space for emptied rack **810**. Vial **104** is picked up by flexible arm **802**, taken to barcode reading station **804** for identification and then placed on mixer/homogenizer station **700** for pH adjustment. Mixer/homogenizer **704** shaft has on it a pH probe connected to pH multimeter **720**, which measures the pH of mixture in vial **104** and controls the addition of acid/base via two valves **718** to reach the set-point value.

In mix vial step **1420,** when the pH of mixture is within the desired range, the mixture in vial **104** is mixed at high shear for two minutes by the mixer/homogenizer **704**. After mixing, the mixer/homogenizers **704** move vertically up till they are out of the vials **104**, move to ultrasonic bath **706** to get washed and then moved to rinse station **708** to get rinsed. Vial **104** is moved back to rack **102** on the rack storage space for emptied rack **810** by flexible arm **802**. The rack **102** is then moved to rack **102** exit point by the flexible arm **802**.

In phase analysis step **1422,** arm **302** transfers rack **102** from rack **102** exit point by flexible arm **802** to rack **102** entry point on phase stability and cloud point station **1000**. Tool head **1004** on this station picks up the **104** from rack **102** with gripper **1006**, takes it to barcode reader **1010** for identification and then puts it on turbidity analysis instrument **1008** for phase analysis.

In determination step **1424,** the analysis results are analyzed by the software and the mixture is classified into categories such as, but not limited to, "Transparent", "Turbid", "Foamy", "Two-phase" etc.

If the mixture in vial **104** is not identified as "Transparent", in rejection step **1426,** it is flagged as "rejected", and moved to rack **102**, reserved for rejected samples, by tool head **1004**. This rack **102**, when filled, is moved to rack **102** exit point by tool head **1004**, picked up by arm **302** and transferred back to the rack and vial storage system **100**.

This brings the system to end point **1438,** the experimental run is considered to be finished in the system.

However, if the mixture in vial **104** is identified as "Transparent" by the instrument **1008,** in storage step **1428,** it is flagged as "passed", and moved to rack **102**, reserved for "passed" samples, by tool head **1004**. This rack **102**, when filled, is moved to rack **102** exit point by tool head **1004**, picked up by arm **302** and transferred back to rack and vial storage system **100** in a space reserved for "passed" samples and stored for 24 hours. In phase analysis step **1430,** after 24 hours, arm **302** picks up rack **102** containing "passed" samples again from rack and vial storage system **100** and transfers them to rack **102** entry point on phase stability and cloud point station **1000**. Tool head **1004** on this station picks up vial **104** from rack **102** with gripper **1006**, takes it to barcode reader **1010** for identification and then puts it on turbidity analysis instrument **1008** for phase analysis.

In second determination step **1432,** the analysis results are again analyzed by the software and the mixture is classified into categories such as, but not limited to "Transparent", "Turbid", "Foamy", "Two-phase" etc.

As before, in second in rejection step **1434,** if the mixture in vial **104** is not identified as "Transparent", then it is flagged as "rejected", and moved to rack **102**, reserved for rejected

samples, by tool head **1004**. This rack **102**, when filled, is moved to rack **102** exit point by tool head **1004**, picked up by arm **302** and transferred back to the rack and vial storage system **100**.

This brings the system to end point **1438,** the experimental run is considered to be finished in the system.

However, if the mixture in vial **104** is identified as "Transparent" by the instrument **1008,** in storage step **1428,** it is flagged as "passed", and moved to rack **102**, reserved for "passed" samples, by tool head **1004**. This rack **102**, when filled, is moved to rack **102** exit point by tool head **1004**, picked up by arm **302** and transferred back to rack and vial storage system **100** in a space reserved for "passed" samples and stored for future analysis.

This brings the system to end point **1438,** the experimental run is considered to be finished in the system

Example Two: Experiment for preparing and testing Suspension Concentrate (SC) emulsion formulations

The objective of this experiment is to prepare a suspension concentrate emulsion formulation, within a certain particle size distribution and viscosity range, containing one active ingredient and two different additives. Successful formulations are then further tested for their chemical and/or biological activity. The steps involved in this experiment are as follows:

1) Add additives in the vial

2) Add active ingredients in the vial

3) Add water in the vial

4) Comminute mixture for 60 minutes

5) Measure particle size distribution

6) If sample is within the desired particle size range, then measure viscosity. Else, reject the sample.

7) If sample is within the desired viscosity range, then the sample is stored for further analysis. Else, the sample is rejected.

In this experiment, the component properties and quantities are assumed to be as those described in the Table below.

Component	Type	Quantity (mL or g)
Additive 1	Low viscosity liquid	1.0
Additive 2	High viscosity liquid	1.0
Active ingredient	Solid	4.0
Water	Low viscosity liquid	4.0

Before starting the experiment, the automated robotic system undergoes the initialization and set-up phase, as was described in the earlier example.

Figure 15 illustrates the flow diagram of the experiment for preparing and testing Suspension Concentrate (SC) emulsion formulation. The various steps involved in executing each block of the flow diagram are described below in detail. We again we note that this description is for illustration purposes only, various embodiments will necessitate various steps in various orders as will be readily seen by the experienced practitioner.

At start of experiment step **1502**, rack **102** containing as many as, but not limited to, six empty vials **104** is picked up by arm **302** and transferred to rack **102** entry point on liquids, suspensions, gels, meltables dispense station **500**. From here, it is moved to rack or dispensing locations **504** by the tool head on liquids, suspensions, gels and meltables dispense station **500**.

In add additive one, step **1504,** the tool head picks up vial **104** from rack **102,** takes it to barcode reader/decapper **508** for barcode scanning and puts it back in rack **102**. Based on the barcode, the control software determines the component, in this case additive one, to be dispensed in vial **104**. For the current experiment, the tool head picks up a disposable pipette from pipette-tip rack space **518**, aspirates 1.0 mL of additive 1 and dispenses it in the appropriate vial **104** in rack **102**. The tool head then moves above trash collection chute **520** to dispose of the pipette tip.

In add additive two, step **1506,** additive two being a high viscosity liquid, is dispensed gravimetrically. The tool head transfers vial **104** from rack **102** to mass balance **516**, which is then initialized and the tare weight determined by the control software. The tool head then picks

up movable gel dispenser **502** containing additive two, brings it over vial **104** and dispenses the additive two in discreet shots of 0.1 g until the balance registers 1.0 g. It then takes movable gel dispenser **502** back to its location and transfers vial **104** back in rack **102**. When all the dispense tasks of liquids, suspensions, gels, meltables dispense station **500** are completed, rack **102** with all vials **104** is transferred to rack **102** exit point on liquids, suspensions, gels and meltables dispense station **500**.

In add active ingredient step **1508,** rack **102** is picked up from rack **102** exit point on liquids, suspensions, gels and meltables dispense station **500** by arm **302** and transferred to rack **102** entry point of solid dispensing station **400** for dispensing active ingredient. From there, vial **104** is first taken to barcode reader **406** for barcode scanning and then placed on mass balance **402** by tool head on solid dispensing station **400**. From the barcode, the control software determines the solid, in this case active ingredient, which is to be dispensed in vial **104**. In the current example, hopper **404** containing active ingredient is picked up by the tool head and 4.0 g of active ingredient is added in appropriate vial **104**. When all solid dispensing tasks are completed, rack **102** is transferred to rack **102** exit point on solid dispensing station **400**.

In add water step **1510,** arm **302** picks up rack **102** from exit point on solid dispensing station **400** and transfers it to rack **102** entry point on normal liquids dispensing and pipetting, and characterization station **600**. The tool head picks up the rack from entry point and transfers it to rack **102** buffer zone. Here, 4.0 mL of water is added volumetrically in vial **104** by the needle on tool head from the active ingredient reservoir connected to the valve and pump system **626**. After adding water, the needle on tool head is rinsed in wash station **628** and rack **102** is then moved to rack **102** exit point on normal liquids dispensing and pipetting, and characterization station **600**.

In comminution step **1512,** beads are first added in vial **104** using a solids canula on the liquids, suspensions, gels, meltables dispense station **500**. Arm **302** transfers rack **102** from exit point on normal liquids dispensing and pipetting, and characterization station **600** to rack **102** entry point on liquids, suspensions, gels and meltables dispense station **500**, from where it is moved to the rack or dispensing locations **504**. The canula on the tool head of liquids, suspensions, gels and meltables dispense station **500** aspirates the required quantity of beads from the comminuting bead source **506** and dispenses them volumetrically into vial **104**. The

rack is then moved to rack **102** exit point on liquids, suspensions, gels and meltables dispense station **500** by the tool head and transferred by arm **302** to rack **102** entry point **808** next to flexible arm **802**. Flexible arm **802** then moves rack **102** to the rack storage space for empty racks **810**. Vial **104** is picked up by flexible arm **802**, taken to capping/decapping/barcode reading/cap supply station **804** for identification and capping. In the capping/decapping/barcode reading/cap supply station **804**, when capping vial **104** in one embodiment, a cap is dispensed from the cap supply and held on the mouth of vial **104** by the tool head. Vial **104** is capped by rotating it around its central vertical axis and then placed in one of comminution locations **904** at defined stop position **908** on vial holder **906** of comminution station **900** by flexible arm **802**. The lid on comminution station **900** is closed and vial holders **906** are then rotated in planetary motion for 60 minutes. At the end of the comminution time, vial holder **906** stops at defined stop position **908**, and vial **104**, is picked up by flexible arm **802** and transferred back to rack **102** in the rack storage space for emptied rack **810**. Rack **102**, when filled, is moved by flexible arm **802** to rack **102** exit point **808**, from where it is transferred by arm **302** to rack **102** entry point on normal liquids dispensing, pipetting, characterization station **600** for bead removal. Vial **104** is moved to barcode reader/capper/decapper **602** by tool head on normal liquids dispensing and pipetting, and characterization station **600**. In one embodiment, the cap on vial **104** is gripped by the barcode reader/capper/decapper **602** tool head and vial **104** is rotated to be de-capped. The cap is disposed of in trash **632** and vial **104** is moved to back to rack **102**. Using special pipettes from the pipette-tip rack space **604**, only the suspension in vial **102** is aspirated and dispensed into new vial **104** in a different rack **102** in the rack buffer space. The barcode of new vial **104** containing the suspension is read at the barcode reader/capper/decapper **602**.The original vial **104** and rack **102** can then be sent to the rack and vial storage system **100** using arm **302** or remain on the station for characterization.

In particle size distribution measuring step **1514,** for measuring the particle size distribution, the tool head picks up a pipette from pipette-tip rack space **604**, aspirates between 0.5 and 1.0 mL of suspension from vial **104** and injects it in the particle-size detector injection port **610**. This port allows dilution of the sample before measuring.

In determination step **1516,** the injected sample is analyzed in the off-deck mounted particle analyzer **618** and the particle size distribution profile is generated. This profile is then

compared by the software with the desired profile and based on the comparison; the samples are classified as "failed" or "passed".

In rejection step **1518,** if the measured particle size distribution of the sample from vial **104** is out of the desired range, then the formulation in that vial **104** is classified as "failed" and is not tested further. It can be transferred in another rack **102**, reserved for "failed" formulation and transferred to rack and vial storage system **100** when it is filled with vials **104**.

This brings the system to end point **1530,** the experimental run is considered to be finished in the system.

If the measured particle size distribution of the sample from vial **104** is within the desired range, then the formulation in that vial **104** is classified as "passed" and its viscosity is measured at both high-shear and low-shear. In high shear viscosity measurement step **1520** and in low sheer viscosity measurement step **1522** the tool head picks up a pipette from pipette-tip rack space **604,** aspirates between 0.5 and 1.0 mL of suspension from vial **104** and injects it in the viscometry injection port(s) **612**. The high shear and low shear measurements are conducted in two different viscometer detectors **620**. After the measurement is complete, viscometry injection port(s) **612** and off deck viscometer detectors **620** are automatically washed and cleaned.

In viscosity determination step **1524,** the measured viscosities are compared with the desired values. If the measurements are within the desired range, then the samples are classified as "passed". If not, they are classified as "failed".

In viscosity rejection step **1526,** samples classified as "failed" are not tested further and can be transferred to another rack **102,** reserved for "failed" formulations . This rack is moved to vial storage system **100** when filled with vials **104**.

This brings the system to end point **1530,** the experimental run is considered to be finished in the system.

If the formulation in vial **104** is classified as "passed", then in storage step **1528** the formulation is moved by the tool head to rack **102,** reserved for "passed" samples. This rack **102,** when filled, is moved to rack **102** exit point by the tool head, picked up by arm **302** and transferred back to rack and vial storage system **100** in a space reserved for "passed" samples and stored for further analysis.

This brings the system to end point **1530,** the experimental run is considered to be finished in the system.

Although the apparatus and process of the present invention has been described in detail for purpose of illustration, it is understood that such detail is solely for that purpose, and variations can be made therein by those skilled in the art without departing from the scope of the invention. The apparatus and operation of the present invention is defined by the following claims.